PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

ELSY, David
Withers & Rogers
Goldings House
2 Hays Lane
London SE1 2HW
GRANDE BRETAGNE

RECEIVED
26 JUL 2004

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

BEST AVAILABLE COPY

Date of mailing *(day/month/year)*	23.07.2004
Applicant's or agent's file reference	IMPORTANT NOTIFICATION
P706097PCT/DE	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/04546	25.04.2003	26.04.2002

Applicant
RAPPOLD, Gudrun, A. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Brandt, M

Tel. +49 89 2399-2926

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P706097PCT/DE	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/04546	International filing date *(day/month/year)* 25.04.2003	Priority date *(day/month/year)* 26.04.2002

International Patent Classification (IPC) or both national classification and IPC

C07K14/47

Applicant

RAPPOLD, Gudrun, A. et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27.10.2003	23.07.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Pilat, D Telephone No. +49 89 2399-8668

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/04546

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnishe the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally fil and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-44 as originally filed

Claims, Numbers

1-13 as originally filed

Drawings, Sheets

1/7-7/7 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☒ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description, pages:

☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 6-9,12

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☒ the claims, or said claims Nos. 6-9,12 are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2,10,11
	No:	Claims	1,3-5,13
Inventive step (IS)	Yes:	Claims	
	No:	Claims	2,10,11
Industrial applicability (IA)	Yes:	Claims	1-5,10-11,13
	No:	Claims	

2. Citations and explanations

   see separate sheet

Ad Section I: Basis of the opinion

1. Reference is made to the following documents:

D1: DATABASE EMBL [Online] EMBL; Homo sapiens BAC clone RP11-461H6 from Y 29 October 1999 (1999-10-29), SULSTON J.E., WILSON R.: "Towards a complete genome sequence" XP002258859 retrieved from EBI Database accession no. AC012502

D2: DATABASE EMBL [Online] EMBL; Homo sapiens BAC clone RP11-75F5 from Y 6 October 1999 (1999-10-06), SULSTON J.E., WILSON R.: "Towards a complete human genome sequence" XP002258860 retrieved from EBI Database accession no. AC011293

D3 "The definition of the Y chromosome growth-control gene (GCY) critical region: Relevance of terminal and interstitial deletions". Kirsch Stefan; Weiss Birgit; Schoen Karin; Rappold Gudrun A Journal of Pediatric Endocrinology and Metabolism , December 2002, VOL - 15, NR - Supplement 5, PG - 1295-1300.

Ad Section III :Non-establishment of opinion

2. **Support and Description (Article 6 PCT and Article 5 PCT).**

Claims 6-9, 12 relate to a GCY protein. However, there is no disclosure throughout the whole application as filed of such a protein. In this respect, the claimed subject-matter does not appear to be adequately disclosed and supported. Since GCY does not identify a specific and unique sequence, any sequence located in the region of Y chromosome within SKY1 and sY83 encoding any protein or protein fragment, comprising prior art as well as proteins which have yet not been identified, falls under the scope of these claims. The same remarks remains valid mutatis mutandis for the expression "ADLY". As a consequence, an assessment with regard to novelty, inventive step and industrial application, cannot be considered reasonable for this claimed subject-matter.

Ad Section V :Reasoned statement under Rule 66.2(a)(ii); citations and explanations supporting such statement

3. **Novelty (Article 33 (2) PCT)**

Direct sequence comparison showed that the prior art BAC clones RP11-75F05 and RP11-461H06 (see D1 and D2), among other sequences, cover the mapped region between Y-STSs SKY8 and SY83 which encompasses a region of roughly 700 kb (see present description p.16 lines 9-13).
These clones are therefore both isolated regions of the Y human chromosome between SKY1 and sY83 which encompasses the Y-specific growth gene GCY.
D1 and D2 anticipate claims 1,3-5,13.

4. Inventive step (Article 33 (3) PCT)

4.1 Document D3 is considered to represent the most relevant state of the art. It discloses the molecular analyses of chromosomes from patients with interstitial Yq deletions. It was establishes that the proximal interval between markers sY78 (DYZ3) and sY83 (DYS11) is the GCY critical interval. The refinement of this localisation led to the definition of 2 non-overlapping critical intervals one between sY78 and sY79, termed GCY interval I and the other sY83 and sY165 termed GCY interval II. Detailed FISH and high density STS analyses confirmed GCY interval I as being the relevant region.
The difference between claim 2 and the present application is that claim 2 identifies a size of the isolated region.
The problem to be solved by the present invention may therefore be regarded as to obtain an isolated fragment of the Y chromosome which lies in between SKY1 and sY83 which encompasses the Y specific growth gene GCY.
To solve the problem posed, the skilled person would have selected any fragment within SKY1 and sY83 and would have arrived at a fragment having a shorter size. No inventive activity can be acknowledged for selecting a particular fragment size among a myriad of other equally suitable fragment sizes. Thus, the solution proposed in claim 2 of the present application cannot be considered as involving an inventive step (Articles 33(3) PCT).

4.2 Document D7 is considered to represent the most relevant state of the art. It discloses the construction of an integrated map which provides a unique resource for the positional cloning of candidate disease genes mapping to Xp22.1. Considering the innate instability of YACs and their susceptibility to chimerism, a high-resolution physical map of more stable clones, such as a PACs or BACs, is needed for the localization and isolation of candidate disease genes mapping to this region. Six overlapping YACs covering about 2 Mb were selected as the basis for the construction of a high-resolution physical and transcript map by combining

sequence tagged site and EST mapping, clone-end sequencing, chromosome walking, and public and private database searches.
D7 differs from the method of claim 11 in that it refers to a method for identifying the GCY gene using STSs associated primers.
The problem to be solved by the present invention may therefore be regarded as to provide a physical map to be capable to position the GCY gene.
In order to solve the problem posed, the skilled person would have carried out the method described in D7 but would have applied the same to the human Y chromosome GCY locus flanked by the markers sY78 and sY83.
The skilled person would therefore have identified new STSs and would have designed new primers to identify naturally occurring deletion in patient having short stature (see reference Vollrath et al. 1992, cited in the present application).
Thus, the solution proposed in claim 11 of the present application cannot be considered as involving an inventive step (Article 33(3) EPC). The same conclusion applies to the selected nucleic acid primers as claimed in claim 10.

Ad Section VI : Certain documents

5 The document D3 was not cited in the international search report.
It is emphasized that the content of the present document may have been orally disclosed at the 33rd International Symposium on Growth Hormone and Growth Factors in Endocrinology and Metabolism; Barcelona, Spain; April 19-20, 2002 (see the following biosis database entry):

TI "The definition of the Y chromosome growth-control gene (GCY) critical region: Relevance of terminal and interstitial deletions.
AU - Kirsch Stefan; Weiss Birgit; Schoen Karin; Rappold Gudrun A
AUAF- Institute of Human Genetics, University of Heidelberg, Im Neuenheimer Feld 328, 69120, Heidelberg, Germany; gudrun_rappold@med.uni-heidelberg.
PUB - Journal of Pediatric Endocrinology and Metabolism
- December 2002
IRN - ISSN 0334-018X
VOL - 15
NR - Supplement 5
PG - 1295-1300
CONF- 33rd International Symposium on Growth Hormone and Growth Factors in Endocrinology and Metabolism; Barcelona, Spain; April 19-20, 2002.